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TOWNSEND and TOWNSEND and CREW LLP

By: Eleanor Taylor

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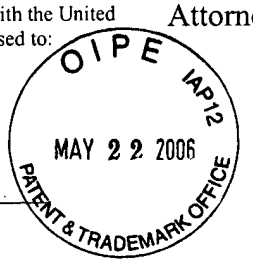

Attorney Docket No.: 018547-050800US
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re application of:	Confirmation No. 5735
WEI-MIN LIU, ET AL.	Examiner: Jerry Lin
Application No.: 09/735,574	Technology Center/Art Unit: 1631
Filed: December 12, 2000	
For: SYSTEMS AND COMPUTER SOFTWARE PRODUCTS FOR COMPARATIVE GENE EXPRESSION ANALYSIS	**APPELLANTS' BRIEF UNDER 37 C.F.R. § 41.37**

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Sir:

Further to the Notice of Appeal filed on November 30, 2005 in the above-referenced application, Appellants submit this Brief on Appeal along with the fee set forth under 37 C.F.R. § 41.37.

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1. REAL PARTY IN INTEREST

Affymetrix, Inc.

2. RELATED APPEALS AND INTERFERENCES

None.

3. STATUS OF CLAIMS

Claims 1-6, 14-19, and 27-32 are pending and appealed. Claims 7-13, 20-26, and 33-39 are cancelled.

4. STATUS OF AMENDMENTS

On November 30, 2005, an amendment after final was filed. Claims 1, 14, and 27 were amended to overcome certain objections.

On December 27, 2005, an Advisory Action was mailed stating that "[i]n light of the amendments, the objections to claims 1, 14, and 27 are withdrawn." (Advisory Action mailed December 27, 2005, page 2). Hence it is understood by Appellants that the amendment after final filed November 30, 2005 has been entered.

An amendment after final is submitted herewith canceling claims 7-13, 20-26, and 33-39. Claims 7-13, 20-26, and 33-39 were previously withdrawn from examination. It is not yet known whether the Examiner will enter the amendment. The listing of claims in CLAIM APPENDIX assumes the amendment will be entered.

5. SUMMARY OF CLAIMED SUBJECT MATTER

Three independent claims 1, 14, and 27 are pending in the present application. Claim 1 is directed to a computer implemented method for calculating a normalization factor (e.g., specification at p. 25, lines 7-17; Figure 3). The implemented method includes providing a first intensity value ($I^{(1)}$) of a probe in a first probe array and a second intensity value ($I^{(2)}$) of said probe in a second probe array (e.g., specification at p. 19, line 2, and p. 23, lines 5-7). The intensity values indicate nucleic acid hybridization (e.g., specification at p. 19, lines 8-13). Additionally, the implemented method includes obtaining the geometric mean (x) of said $I^{(1)}$ and said $I^{(2)}$ (e.g., specification, p. 23, line 7). Moreover, the implemented method includes calculating said normalization factor according to $f(x) = e^{h(x)}$, wherein said $h(x)$ is derived from referential intensities

from said first and second probe arrays (e.g., specification, p. 23, lines 8-9, and p. 21, line 17 through p. 22, line 15). Also, the implemented method includes using said normalization factor for gene expression analysis and outputting the result of said analysis (e.g., specification, p. 24, lines 11-23).

Claim 14 is directed to a system for calculating a normalization factor (e.g., specification, p. 16, lines 17-20, and p. 17, line 15 through p. 18, line 3; Figure 1, reference character 1). The system includes a processor (e.g., specification, p. 18, line 7; Figure 2, reference character 50). Additionally, the system includes a memory coupled with the processor, the memory storing a plurality of machine instructions that cause the processor to perform a plurality of logical steps when implemented by the processor (e.g., specification, p. 17, lines 18-21; Figures 2, reference characters 50, 52, 58, and 60). The logical steps include providing a first intensity value ($I^{(1)}$) of a probe in a first probe array and a second intensity value ($I^{(2)}$) of said probe in a second probe array (e.g., specification at p. 19, line 2, and p. 23, lines 5-7). The intensity values indicate nucleic acid hybridization (e.g., specification at p. 19, lines 8-13). Additionally, the logic steps include obtaining the geometric mean (x) of said $I^{(1)}$ and said $I^{(2)}$ (e.g., specification, p. 23, line 7). Moreover, the logic steps include calculating said normalization factor according to $f(x) = e^{h(x)}$, wherein said $h(x)$ is derived from referential intensities from said first and second probe arrays (e.g., specification, p. 23, lines 8-9, and p. 21, line 17 through p. 22, line 15). Also, the logic steps include using said normalization factor for gene expression analysis and outputting the result of said analysis (e.g., specification, p. 24, lines 11-23).

Claim 27 is directed to a computer software product for calculating a normalization factor (e.g., specification, p. 16, lines 17 through p. 17, line 1, p. 17, lines 7-14, p. 18, lines 14-16, and p. 19, lines 13-14). The computer software product includes computer program code for providing a first intensity value ($I^{(1)}$) of a probe in a first probe array and a second intensity value ($I^{(2)}$) of said probe in a second probe array (e.g., specification at p. 19, line 2, and p. 23, lines 5-7). The intensity values indicate nucleic acid hybridization (e.g., specification at p. 19, lines 8-13). Additionally, the computer software product includes computer program code for obtaining the geometric mean (x) of said ($I^{(1)}$) and said ($I^{(2)}$) (e.g., specification, p. 23, line 7). Moreover, the computer software product includes computer program code for calculating said normalization factor according to $f(x) = e^{h(x)}$, wherein said $h(x)$ is derived from referential intensities from said first and

second probe arrays (e.g., specification, p. 23, lines 8-9, and p. 21, line 17 through p. 22, line 15). Also, the computer software product includes computer program code for using said normalization factor for gene expression analysis and outputting the result of said analysis (e.g., specification, p. 24, lines 11-23). Additionally, the computer product includes a computer readable medium for storing said codes (e.g., specification, p. 16, lines 17 through p. 17, line 1).

6. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

6.1. Whether claims 1-6, 14-19, and 27-32 are directed to non-statutory subject matter 35 U.S.C. 101.

6.2. Whether claims 1-6, 14-19, and 27-32 would have been obvious under 35 U.S.C. 103(a) over U.S. Patent No. 6,470,277 (Chin) in view of the legal decision of *In re Gulack*, 703 F.2d 1381, 1385, 217 USPQ 401, 404 (Fed. Cir. 1983).

7. ARGUMENT

7.1. Whether Claims 1-6, 14-19, and 27-32 are Directed to Non-Statutory Subject Matter under 35 U.S.C. 101

35 U.S.C. 101 broadly defines the patentable subject mater as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

"In choosing such expansive terms as 'manufacture' and 'composition of matter,' modified by the comprehensive 'any,' Congress plainly contemplated that the patent laws would be given wide scope." *See* Diamond v. Chakrabarty, 447 U.S. 303, 308, 206 USPQ 193, 197 (1980). "Congress intended statutory subject matter to 'include anything under the sun that is made by man.'" *See id.* at 309, 206 USPQ at 197 (citing S.Rep.No.1979, 82d Cong., 2d Sess., 5 (1952); H.R.Rep.No.1923, 82d Cong., 2d Sess., 6 (1952)).

This broad perspective has been embraced by the Federal Circuit. *See* MPEP, § 2106.IV.A. In *State Street Bank & Trust Co. v. Signature Financial Group, Inc.*, the Federal Circuit clearly stated that:

> the mere fact that a claimed invention involves inputting numbers, calculating numbers, outputting numbers, and storing numbers, in and of itself, would not render it nonstatutory subject matter, unless, of course, its operation does not produce a 'useful, concrete and tangible result.' 149 F.3d 1368, 1374, 47 USPQ2d 1596, 1602 (Fed. Cir. 1998).

As an example, "[a] claimed process is clearly statutory if it results in a physical transformation outside the computer, i.e., falls into one or both of the following specific categories ('safe harbors')." *See* MPEP, § 2106.IV.B.2(b). These safe harbors include independent physical acts (post-computer process activity) and manipulating of data representing physical objects or activities (pre-computer process activity). See MPEP, § 2106.IV.B.2(b)(i). If a claim does not clearly fall into either safe harbor, further inquiry needs to be performed to determine whether the claim nonetheless produces a useful, concrete and tangible result.

7.1.1. Claims 1-6, 14-19, and 27-32 are Directed to Statutory Subject Matter Because These Claims Recite Manipulation of Data Representing Physical Objects or Activities (Pre-Computer Process Activity)

The pre-computer process activity includes transforming measurements of physical objects or activities outside the computer into computer data. *See* MPEP, § 2106.IV.B.2.(b)(i) (citing, among others, *In re Abele*, 684 F.2d 902, 214 USPQ 682 (CCPA 1982)).

In *In re Abele*, the court was faced with the following two claims:

> 5. A method of displaying data in a field comprising the steps of calculating the difference between the local value of the data at a data point in the field and the average value of the data in a region of the field which surrounds said point for each point in said field, and displaying the value of said difference as a signed gray scale at a point in a picture which corresponds to said data point.
>
> 6. The method of claim 5 wherein said data is X-ray attenuation data produced in a two dimensional field by a computed tomography scanner. *See id.* at 908, 214 USPQ at 687.

In response, the court "conclude[d] that claim 5 is directed solely to the mathematical algorithm portion of appellants' invention and is, thus, not statutory subject matter under s 101". But the court "reach[ed] the opposite conclusion with respect to claim 6." *See id.* (emphasis added).

Specifically, "claim 6 presents data gathering steps not dictated by the algorithm but by other limitations which require certain antecedent steps." *See id.* Hence "[t]he improvement ... resides in the application of a mathematical formula within the context of a process which encompasses significantly more than the algorithm alone." *See id.* at 909, 214 USPQ at 688 (emphasis added). Therefore, claim 6 is directed to statutory subject matter under 35 U.S.C. 101.

Similar to claim 6 in *In re Abele*, claims 1-6, 14-19, and 27-32 of the present application are also directed to statutory subject matter. More particularly, these claims each recite an "application of a mathematical formula within the context of a process which encompasses significantly more than the algorithm alone." *See id.* For example, the three independent claims 1, 14, and 27 each state "wherein the intensity values indicate nucleic acid hybridization", and "referential intensities from said first and second probe arrays." Hence these claims present "data gathering steps not dictated by the algorithm but by other limitations which require certain antecedent steps." *See id.* at 908, 214 USPQ at 687.

For example, the data gathering steps of "the intensities values" include applying a cRNA sample from cancerous cells to one probe array, applying a cRNA sample from normal cells to another probe array, and reading fluorescent intensities from probes in the arrays. (specification, p.18, line 18-20, p. 20, lines 6-9). In another example, the data gathering steps of "referential intensities from the first and second probe arrays" include obtaining signals from normalization controls after hybridization (specification, p. 20, lines 3-4).

Hence, like claim 6 of *In re Abele*, claims 1-6, 14-19, and 27-32 of the present invention each refer to a pre-computer process activity. The pre-computer process activity transforms measurements of physical objects or activities outside the computer into computer data. Therefore, claims 1-6, 14-19, and 27-32 are directed to statutory subject matter for at least these reasons.

7.1.2. Claims 1-6, 14-19, and 27-32 are Directed to Statutory Subject Matter Because These Claims Produce a Useful, Concrete, and Tangible Result

In *State Street*, the Federal Circuit applied the "useful, concrete, and tangible result" test in determining whether claim 1 of U.S. Patent No. 5,193,056 is directed to statutory subject matter. *See* 149 F.3d at 1375, 47 USPQ2d at 1602. The Federal Circuit held:

> the transformation of data, representing discrete dollar amounts, by a machine through a series of mathematical calculations into a final share price, constitutes a practical application of a mathematical algorithm, formula, or calculation, because it produces "a useful, concrete and tangible result"-a final share price momentarily fixed for recording and reporting purposes and even accepted and relied upon by regulatory authorities and in subsequent trades. *See id.* at 1373, 47 USPQ2d at 1601 (emphasis added).

Additionally, the Federal Circuit ruled:

> For purpose of our analysis, as noted above, claim 1 is directed to a machine programmed with the Hub and Spoke software and admittedly produces a "useful, concrete, and tangible result." Alappat, 33 F.3d at 1544, 31 USPQ2d at 1557. This renders it statutory subject matter, even if the useful result is expressed in numbers, such as price, profit, percentage, cost, or loss. *See id.* at 1375, 47 USPQ2d at 1602 (emphasis added).

Similar to claim 1 in *State Street*, claims 1-6, 14-19, and 27-32 of the present application each produce "a useful, concrete, and tangible result." Specifically, each independent claims 1, 14, and 27 recites "using said normalization factor for gene expression analysis and outputting the result of said analysis." The use of the normalization factor can, for example, "adjust signals from probe arrays (*e.g.*, intensity values) to compensate for array to array variations" (specification, p. 19, lines 1-2). Additionally, the output of the result of the analysis can, for example, be used to determine whether the expression of gene is increased in one sample in comparison with another sample (specification, p. 24, lines 17-22). Such determination may lead to the development of new drugs and new diagnostic tools (specification, p. 3, lines 11-13).

Hence, like claim 1 in *State Street*, claims 1-6, 14-19, and 27-32 of the present application are directed to statutory subject matter for at least these reasons.

7.1.3. Appellants Respectfully Rebut Examiner's Comments

In Final Office Action mailed June 1, 2005, the Examiner maintained the rejection from the previous Office Action mailed March 25, 2004 (Final Office Action, p.3). Additionally, the Examiner asserted the claim limitation of "using said normalization factor for gene analysis and outputting the result of said analysis" cannot not place the claims 1-6, 14-19, and 27-32 into the realm of statutory subject matter. In more detail, the Examiner appears to have rejected claims 1-6, 14-19, and 27-32 because the claims do not require performance of a result outside of a computer and the claims do not result in any physical transformation outside of the computer (Final Office Action, p. 3, and Office Action dated March 25, 2004, p.2). Appellants disagree with the Examiner.

First, the case law does not require that a claim directed to the statutory subject matter must include performance of a result outside of a computer, or any physical transformation outside of the computer. In contrast, a claim is statutory so long as it produces "a useful, concrete and tangible result." *See* State Street, 149 F.3d at 1374, 47 USPQ2d at 1602. Hence a claim can be patentable even if the claim does not include a result outside of a computer or any physical transformation outside of the computer.

MPEP § 2106.IV.B cited by the Examiner does not require, for statutory subject matter, performance of a result outside of a computer or any physical transformation outside of the computer. What is stated in MPEP 2106.IV.B is that "[a] claimed process is clearly statutory if it results in a physical transformation outside the computer, i.e., falls into one or both of the following specific categories ('safe harbors')." *See* MPEP, § 2106.IV.B.2(b). Hence "results in a physical transformation outside computer" is asserted to be sufficient for statutory subject matter, but it is not considered being necessary. In fact, MPEP, § 2106.IV.B.2(b)(i) also states "[i]f a claim does not clearly fall into one or both of the safe harbors, the claim may still be statutory if it is limited to a practical application in the technological arts." As held in *State Street*, a claim is directed to a statutory subject matter if it produces "a useful, concrete and tangible result." *See* 149 F.3d at 1374, 47 USPQ2d at 1602.

Second, claims 1-6, 14-19, and 27-32 of the present application satisfy at least one of the two safe harbors as related to a physical transformation outside the computer. Like claim 6 of *In re Abele*, the pending claims of the present application refers to a pre-computer process activity that

transforms measurements of physical objects or activities outside the computer into computer data. Therefore, claims 1-6, 14-19, and 27-32 are statutory for at least these reasons.

Furthermore, claims 1-6, 14-19, and 27-32 of the present application produce a useful, concrete, and tangible result, regardless of whether these claims each result in a physical transformation outside the computer. For example, the use of the normalization factor can "adjust signals from probe arrays (*e.g.*, intensity values) to compensate for array to array variations" (specification, p. 19, lines 1-2). Additionally, the output of the result of the analysis can, for example, be used to determine whether the expression of gene is increased in one sample in comparison with another sample (specification, p. 24, lines 17-22). Such determination may lead to the development of new drugs and new diagnostic tools (specification, p. 3, lines 11-13).

Hence claims 1-6, 14-19, and 27-32 of the present application are directed to statutory subject matter.

7.2. Whether Claims 1-6, 14-19, and 27-32 would have been obvious under 35 U.S.C. 103(a) over Chin in view of the legal decision of *In re Gulack*

Claims 1-6, 14-19, and 27-32 would not have been obvious under 35 U.S.C. 103(a) over Chin in view of the legal decision of *In re Gulack*. Chin fails to disclose or suggest all limitations for each of claims 1-6, 14-19, and 27-32. The claim limitations not disclosed or suggested by Chin should be accorded patentability weight, and thus render claims 1-6, 14-19, and 27-32 patentable over Chin.

7.2.1. Examiner's Rational for Rejecting Claims 1-6, 14-19, and 27-32 under 35 U.S.C. 103(a)

In Final Office Action mailed June 1, 2005, the Examiner maintained the rejection from the previous Office Action mailed March 25, 2004 (Final Office Action, p. 4). The Examiner emphasized that "the mathematical steps in the claims still do not control any function, such as a practical action or a physical transformation and remain nonfunctional. Nonfunctional descriptive material in a claims[sic] does not distinguish the prior art in terms of patentability. Thus these steps do not distinguish over the normalization factor practice as in the reference" (Final Office Action, p. 4).

Specifically, the Examiner appear to have conceded that Chin fails to disclose or suggest all limitations for each of claims 1-6, 14-19, and 27-32. But the Examiner asserted that the limitations not disclosed or suggested by Chin are nonfunctional descriptive material and thus cannot distinguish the claims over Chin. To support this assertion, the Examiner specifically cited *In re Gulack* and MPEP § 2106.VI (Final Office Action, p. 4). Appellants disagree with the Examiner's assertion.

7.2.2. Claim Limitations Not Disclosed or Suggested by Chin are *Not* Non-Function Descriptive Material

Chin does not disclose or suggest all limitations for each of claims 1-6, 14-19, and 27-32. Specifically, each independent claims 1, 14, and 27 recites "calculating said normalization factor according to: $f(x) = e^{h(x)}$, wherein said $h(x)$ is derived from referential intensities from said first and second probe arrays." In contrast, Chin discloses "the local background or normalization factor" and "the arithmetic mean of the background or normalized data" (Chin, col. 16, lines 14-15 and 39-40). Hence Chin fails to disclose or suggest at least "calculating said normalization factor according to: $f(x) = e^{h(x)}$, wherein said $h(x)$ is derived from referential intensities from said first and second probe arrays."

These claim limitations are not non-functional descriptive material. Non-functional descriptive material is discussed in MPEP § 2106.IV.B.1(b), which is referred to by MPEP § 2106.VI. MPEP § 2106.IV.B.1(b) states:

> Where certain types of descriptive material, such as music, literature, art, photographs and mere arrangements or compilations of facts or data, are merely stored so as to be read or outputted by a computer without creating any functional interrelationship, either as part of the stored data or as part of the computing processes performed by the computer, then such descriptive material alone does not impart functionality either to the data as so structured, or to the computer. (emphasis added).

In contrast, the claim limitations "calculating said normalization factor according to: $f(x) = e^{h(x)}$, wherein said $h(x)$ is derived from referential intensities from said first and second probe arrays" can cause a computer or a processor to perform a specific function as part of the computing processes. Hence, these claim limitations imparts functionality to the computer or the processor.

In Final Office Action mailed June 1, 2005, the Examiner asserted that "the mathematical steps in claims still do not control any function, such as a practical action or a physical transformation and remain nonfunctional." But the claimed mathematical step performed by a computer or a processor is functional. The court in *In re Gulack* held that "[t]he bare presence or absence of a specific functional relationship, without further analysis, is not dispositive of obviousness. Rather, the critical question is whether there exists any new and unobvious functional relationship between the printed matter and the substrate." *See* 703 F.2d 1381, 1386, 217 USPQ 401, 404 (Fed. Cir. 1983). Here, in the present application, the claim limitations "calculating said normalization factor according to: $f(x) = e^{h(x)}$, wherein said $h(x)$ is derived from referential intensities from said first and second probe arrays" can cause the computer or the processor to perform a specific computing process and thus create a new and unobvious function relationship between the computer program and the computer or the processor.

Hence the claim limitations not disclosed or suggested by Chin are not non-functional descriptive material and should be accorded patentable weight.

7.2.3. Examiner Has Failed to Establish a Prima Facie Case of Obviousness

As discussed above, Chin fails to disclose or suggest all limitations for each of claims 1-6, 14-19, and 27-32. The claim limitations not disclosed or suggested by Chin are not non-function descriptive material, and should be accorded patentable weight. Hence the Examiner has failed to establish a prima facie case of obviousness as required by the Patent and Trademark Office.

8. CONCLUSION

For these reasons, it is respectfully submitted that the rejections of claims 1-6, 14-19, and 27-32 under 35 U.S.C. § 101 and 35 U.S.C. § 103 should be reversed.

Respectfully submitted,

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9. CLAIM APPENDIX

1. (previously presented) A computer implemented method for calculating a normalization factor comprising:

providing a first intensity value ($I^{(1)}$) of a probe in a first probe array and a second intensity value ($I^{(2)}$) of said probe in a second probe array, wherein the intensity values indicate nucleic acid hybridization;

obtaining the geometric mean (x) of said $I^{(1)}$ and said $I^{(2)}$;

calculating said normalization factor according to:

$f(x) = e^{h(x)}$, wherein said $h(x)$ is derived from referential intensities from said first and second probe arrays; and

using said normalization factor for gene expression analysis and outputting the result of said analysis.

2. (original) The method of Claim 1 wherein said $h(x)$ is derived by relating geometric means (x_i') of first referential intensities ($RI_i^{(1)}$) in the first probe array and second referential intensities ($RI_i^{(2)}$) in the second probe array to:

$$y_i = \log\left(\frac{RI_i^{(1)}}{RI_i^{(2)}}\right).$$

3. (original) The method of Claim 2 wherein said relating comprising:

sorting (x_i, y_i) pairs according to x_i into a plurality (m number) of bins with no overlapping;

computing medians ($\bar{x}_k$) of x_i's and medians ($\bar{y}_k$) of y_i's for each bin; and

interpolating said medians ($\bar{x}_k$, $\bar{y}_k$).

4. (original) The method of Claim 3 wherein said bins are of approximately equal size.

5. (original) The method of Claim 4 wherein said $h(x)$ is:

$$h(x)=\begin{cases}\overline{y}_1, & if\ x\le \overline{x}_1\\ w\overline{y}_1+(1-w)\overline{y}_{1+1}, & if\ x\in(\overline{x}_1,\overline{x}_1+1),\ w=\dfrac{\overline{x}_1+1-x}{\overline{x}_1+1-\overline{x}_1} \quad ,i=1,\ldots,m-1,\\ \overline{y}_m, & if\ x>\overline{x}_m.\end{cases}$$

6. (original) The method of Claim 5 wherein said m is 3.

14. (previously presented) A system for calculating a normalization factor comprising:

a processor; and

a memory coupled with the processor, the memory storing a plurality of machine instructions that cause the processor to perform a plurality of logical steps when implemented by the processor, the logical steps comprising:

providing a first intensity value ($I^{(1)}$) of a probe in a first probe array and a second intensity value ($I^{(2)}$) of said probe in a second probe array, wherein the intensity values indicate nucleic acid hybridization;

obtaining the geometric mean (x) of said $I^{(1)}$ and said $I^{(2)}$;

calculating said normalization factor according to:

$f(x) = e^{h(x)}$, wherein said $h(x)$ is derived from referential intensities from said first and second probe arrays; and

using said normalization factor for gene expression analysis and outputting the result of said analysis.

15. (original) The system of Claim 14 wherein said *h(x)* is derived by relating geometric means (*xi'*) of first referential intensities ($RI_i^{(1)}$) in the first probe array and second referential intensities ($RI_i^{(2)}$) in the second probe array to:

$$y_i = \log\left(\frac{RI_i^{(1)}}{RI_i^{(2)}}\right).$$

16. (original) The system of Claim 15 wherein said relating comprising:

sorting (x_i, y_i) pairs according to x_i into a plurality (m number) of bins with no overlapping;

computing medians ($\overline{x}_k$) of x_i's and medians ($\overline{y}_k$) of y_i's for each bin; and

interpolating said medians ($\overline{x}_k$, $\overline{y}_k$).

17. (original) The system of Claim 16 wherein said bins are of approximately equal size.

18. (original) The system of Claim 17 wherein said *h(x)* is:

$$h(x) = \begin{cases} \overline{y}_1, & \text{if } x \le \overline{x}_1 \\ w\overline{y}_1 + (1-w)\overline{y}_{1+1}, & \text{if } x \in (\overline{x}_1, \overline{x}_1 + 1),\ w = \dfrac{\overline{x}_1 + 1 - x}{\overline{x}_1 + 1 - \overline{x}_1} \quad ,i = 1,\ldots,m-1, \\ \overline{y}_m, & \text{if } x > \overline{x}_m. \end{cases}$$

19. (original) The system of Claim 18 wherein said m is 3.

27. (previously presently) A computer software product for calculating a normalization factor comprising:

computer program code for providing a first intensity value ($I^{(1)}$) of a probe in a first probe array and a second intensity value ($I^{(2)}$) of said probe in a second probe array, wherein the intensity values indicate nucleic acid hybridization;

computer program code for obtaining the geometric mean (x) of said $I^{(1)}$ and said $I^{(2)}$;

computer program code for calculating said normalization factor according to:

$f(x) = e^{h(x)}$, wherein said $h(x)$ is derived from referential intensities from said first and second probe arrays; and

computer program code for using said normalization factor for gene expression analysis and outputting the result of said analysis; and

a computer readable medium for storing said codes.

28. (original) The computer software product of Claim 27 wherein said $h(x)$ is derived by relating geometric means (x_i') of first referential intensities ($RI_i^{(1)}$) in the first probe array and second referential intensities ($RI_i^{(2)}$) in the second probe array to:

$$y_i = \log\left(\frac{RI_i^{(1)}}{RI_i^{(2)}}\right).$$

29. (original) The computer software product of Claim 28 wherein said code for relating comprising:

computer program code for sorting (x_i, y_i) pairs according to x_i into a plurality (m number) of bins with no overlapping;

computer program code for computing medians ($\overline{x}_k$) of $x_i's$ and medians ($\overline{y}_k$) of $y_i's$ for each bin; and

computer program code for interpolating said medians ($\overline{x}_k, \overline{y}_k$).

30. (original) The computer software product of Claim 29 wherein said bins are of approximately equal size.

31. (original) The computer software product of Claim 30 wherein said *h(x)* is:

$$h(x) = \begin{cases} \overline{y}_1, & if\ x \le \overline{x}_1 \\ w\overline{y}_1 + (1-w)\overline{y}_{1+1}, & if\ x \in (\overline{x}_1, \overline{x}_1 + 1),\ w = \dfrac{\overline{x}_1 + 1 - x}{\overline{x}_1 + 1 - \overline{x}_1} \\ \overline{y}_m, & if\ x > \overline{x}_m. \end{cases} \quad ,i = 1, \ldots, m-1,$$

32. (original) The computer software product of Claim 31 wherein said *m* is 3.

10. EVIDENCE APPENDIX

None.

11. RELATED PROCEEDINGS APPENDIX

None.

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TOWNSEND and TOWNSEND and CREW LLP

By: Eleanor J. Taylor

PATENT
Attorney Docket No.: 018547-050800US
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	Confirmation No. 5735
Wei-min Liu et al.	Examiner: Jerry Lin
Application No.: 09/735,574	Technology Center/Art Unit: 1631
Filed: December 12, 2000	AMENDMENT UNDER 37 C.F.R. § 41.37
For: SYSTEMS AND COMPUTER SOFTWARE PRODUCTS FOR COMPARATIVE GENE EXPRESSION ANALYSIS	
Customer No.: 33494	

Mail Stop Appeal Brief - Patents
Commissioner for Patents
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Sir:

Under 37 C.F.R. § 41.37, please enter the following amendments and remarks:

Amendments to the Claims are reflected in the listing of claims which begins on page 2 of this paper.

Remarks/Arguments begin on page 8 of this paper.

Amendments to the Claims:

This listing of claims will replace all prior versions, and listings of claims in the application:

Listing of Claims:

1. (previously presented) A computer implemented method for calculating a normalization factor comprising:

providing a first intensity value ($I^{(1)}$) of a probe in a first probe array and a second intensity value ($I^{(2)}$) of said probe in a second probe array, wherein the intensity values indicate nucleic acid hybridization;

obtaining the geometric mean (x) of said $I^{(1)}$ and said $I^{(2)}$;

calculating said normalization factor according to:

$f(x) = e^{h(x)}$, wherein said $h(x)$ is derived from referential intensities from said first and second probe arrays; and

using said normalization factor for gene expression analysis and outputting the result of said analysis.

2. (original) The method of Claim 1 wherein said $h(x)$ is derived by relating geometric means (x_i') of first referential intensities ($RI_i^{(1)}$) in the first probe array and second referential intensities ($RI_i^{(2)}$) in the second probe array to:

$$y_i = \log\left(\frac{RI_i^{(1)}}{RI_i^{(2)}}\right).$$

3. (original) The method of Claim 2 wherein said relating comprising:

sorting (x_i, y_i) pairs according to x_i into a plurality (m number) of bins with no overlapping;

computing medians ($\overline{x}_k$) of x_i's and medians ($\overline{y}_k$) of y_i's for each bin; and

interpolating said medians ($\overline{x}_k$, $\overline{y}_k$).

4. (original) The method of Claim 3 wherein said bins are of approximately equal size.

5. (original) The method of Claim 4 wherein said $h(x)$ is:

$$h(x)=\begin{cases}\overline{y}_1, & \text{if } x \le \overline{x}_1 \\ w\overline{y}_1+(1-w)\overline{y}_{1+1}, & \text{if } x \in (\overline{x}_1, \overline{x}_1+1),\ w=\dfrac{\overline{x}_1+1-x}{\overline{x}_1+1-\overline{x}_1} \\ \overline{y}_m, & \text{if } x > \overline{x}_m.\end{cases} \quad ,i=1,\ldots,m-1,$$

6. (original) The method of Claim 5 wherein said m is 3.

7. - 13. (canceled)

14. (previously presented) A system for calculating a normalization factor comprising:

a processor; and

a memory coupled with the processor, the memory storing a plurality of machine instructions that cause the processor to perform a plurality of logical steps when implemented by the processor, the logical steps comprising:

providing a first intensity value ($I^{(1)}$) of a probe in a first probe array and a second intensity value ($I^{(2)}$) of said probe in a second probe array, wherein the intensity values indicate nucleic acid hybridization;

obtaining the geometric mean (x) of said $I^{(1)}$ and said $I^{(2)}$;

calculating said normalization factor according to:

$f(x) = e^{h(x)}$, wherein said $h(x)$ is derived from referential intensities from said first and second probe arrays; and

using said normalization factor for gene expression analysis and outputting the result of said analysis.

15. (original) The system of Claim 14 wherein said $h(x)$ is derived by relating geometric means (xi') of first referential intensities ($RI_i^{(1)}$) in the first probe array and second referential intensities ($RI_i^{(2)}$) in the second probe array to:

$$y_i = \log\left(\frac{RI_i^{(1)}}{RI_i^{(2)}}\right).$$

16. (original) The system of Claim 15 wherein said relating comprising:

sorting (x_i, y_i) pairs according to x_i into a plurality (m number) of bins with no overlapping;

computing medians ($\overline{x}_k$) of x_i's and medians ($\overline{y}_k$) of y_i's for each bin; and

interpolating said medians ($\overline{x}_k$, $\overline{y}_k$).

17. (original) The system of Claim 16 wherein said bins are of approximately equal size.

18. (original) The system of Claim 17 wherein said *h(x)* is:

$$h(x)=\begin{cases}\overline{y}_1, & if\ x\le \overline{x}_1\\ w\overline{y}_1+(1-w)\overline{y}_{1+1}, & if\ x\in(\overline{x}_1,\overline{x}_1+1),\ w=\dfrac{\overline{x}_1+1-x}{\overline{x}_1+1-\overline{x}_1} \quad ,i=1,\ldots,m-1,\\ \overline{y}_m, & if\ x>\overline{x}_m.\end{cases}$$

19. (original) The system of Claim 18 wherein said *m* is 3.

20. - 26. (canceled)

27. (previously presently) A computer software product for calculating a normalization factor comprising:

computer program code for providing a first intensity value ($I^{(1)}$) of a probe in a first probe array and a second intensity value ($I^{(2)}$) of said probe in a second probe array, wherein the intensity values indicate nucleic acid hybridization;

computer program code for obtaining the geometric mean (*x)* of said $I^{(1)}$ and said $I^{(2)}$;

computer program code for calculating said normalization factor according to:

$f(x) = e^{h(x)}$, wherein said *h(x)* is derived from referential intensities from said first and second probe arrays; and

computer program code for using said normalization factor for gene expression analysis and outputting the result of said analysis; and

a computer readable medium for storing said codes.

28. (original) The computer software product of Claim 27 wherein said *h(x)* is derived by relating geometric means (x_i') of first referential intensities ($RI_i^{(1)}$) in the first probe array and second referential intensities ($RI_i^{(2)}$) in the second probe array to:

$$y_i = \log\left(\frac{RI_i^{(1)}}{RI_i^{(2)}}\right).$$

29. (original) The computer software product of Claim 28 wherein said code for relating comprising:

computer program code for sorting (x_i, y_i) pairs according to x_i into a plurality (m number) of bins with no overlapping;

computer program code for computing medians ($\overline{x}_k$) of $x_i's$ and medians ($\overline{y}_k$) of $y_i's$ for each bin; and

computer program code for interpolating said medians ($\overline{x}_k, \overline{y}_k$).

30. (original) The computer software product of Claim 29 wherein said bins are of approximately equal size.

31. (original) The computer software product of Claim 30 wherein said *h(x)* is:

$$h(x)=\begin{cases}\overline{y}_1, & \text{if } x \le \overline{x}_1 \\ w\overline{y}_1+(1-w)\overline{y}_{1+1}, & \text{if } x \in (\overline{x}_1, \overline{x}_1+1),\ w=\dfrac{\overline{x}_1+1-x}{\overline{x}_1+1-\overline{x}_1} \\ \overline{y}_m, & \text{if } x > \overline{x}_m.\end{cases} \quad ,i=1,\ldots,m-1,$$

32. (original) The computer software product of Claim 31 wherein said m is 3.

33. - 39. (canceled)

REMARKS/ARGUMENTS

This Amendment Under 37 C.F.R. § 41.37 is for the purpose of canceling withdrawn claims 7-13, 20-26, and 33-39. Upon entry of this Amendment, claims 1-6, 14-19, and 27-32 are pending and appealed.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-326-2400.

Respectfully submitted,

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